However, Graham J. Moore teaches the use of NMR techniques which are employed to evaluate tertiary structures of biological active ligands that has a molecular weight of <500 or >2000 Daltons (col. 3, lines 1-46) and also includes through-bond coupling patterns within a molecule (col. 13, lines 22-50). Preferably, when analyzing by NMR, the ligand should have a molecular weight of less than 3,000 Daltons.

It would have been obvious to one of ordinary skill in the art to modify the teachings of Yabuki et al to include the use of small molecular weight ligands to evaluate tertiary structures of biological active ligands as taught by Graham J. Moore. Further, absent evidence to the contrary, the range recited in the instant claims from 50-1000 Daltons is viewed as mere optimization of the prior art assay.

Applicants respectfully traverse the rejection in view of the following comments.

Claim 1 is directed to a method for identifying a binder molecule by carrying out a series of steps that include the following: generating a first nuclear magnetic resonance (NMR) spectrum of a labeled polypeptide or protein; generating a second NMR spectrum of the labeled polypeptide or protein that has been contacted with a potential binder molecule having a molecular mass of from 50 to 1000 Da; and comparing the first and second NMR spectra to identify a change of signals that indicates an interaction between a potential binder molecule and the labeled polypeptide or protein.

Yabuki describes using a dual amino acid-selective labeling method for investigating structures of proteins and protein complexes. In particular, Yabuki describes the use of a dual amino acid labeling technique to investigate the nature of the interaction between two proteins (Ras and Raf) that were known to bind to each other. Because Yabuki is not concerned with using the labeling technique to screen for and identify a molecule that binds to a given protein, the skilled artisan would have had no reason to modify the methods of Yabuki to test candidate compounds for their ability to bind to Ras or any other protein. Furthermore, none of the references of record describe a low molecular weight compound (i.e., having a molecular mass of from 50 to 1000 Da, as is required by the claims) that was known to bind to Ras that the skilled artisan might have even attempted to use in the method of Yabuki in place of Raf to investigate the nature of the Ras-ligand interaction. Because Yabuki does not describe a

screening assay for potential binder molecules, there would have been no basis or rationale for the skilled artisan to "optimize" the methods of Yabuki by, for example, replacing Raf (a known ligand of Ras) with a molecule having a molecular mass of from 50 to 1000 Da. Yabuki describes a dual amino acid-selective labeling method using a protein and a known binding partner and gives no hint that low molecular weight compounds having no known binding ability should be replaced in the method.

Moore does not add what is lacking in Yabuki. Moore describes methods for modeling biologically active ligands and designing mimetics of such ligands. Moore does not describe a molecule having a molecular mass of from 50 to 1000 Da as having the ability to bind to Ras or any other protein described in Yabuki. Furthermore, nothing in Moore suggests modifying the protein structure analysis method of Yabuki and converting it into a screening method that compares a first NMR spectra (of a labeled polypeptide or protein) and a second NMR spectra (of the labeled polypeptide or protein that has been contacted with a potential binder molecule having a molecular mass of from 50 to 1000 Da) and identifies a change of signals indicating that an interaction between the potential binder molecule and the labeled polypeptide or protein.

In light of these comments, applicants respectfully submit that the combination of Yabuki and Moore do not render the claimed invention obvious and request that the Examiner withdraw the rejection.

On pages 5-6 of the Office Action, the Examiner rejected claims 2, 3, 6, and 7 as allegedly obvious over Yabuki in view of Moore and WO 97/18471. According to the Examiner,

> [i]t would have been obvious to one of ordinary skill in the art to incorporate a comparison method of the various assays as taught by Fesik et al into the method of Yabuki et al in view of Graham J. Moore to compare the binding of ligands to various biomolecules determined by NMR and to also observe chemical shifts from observed by 2-D NMR techniques.

The Examiner also stated that

> the WO 97/18471 reference teach the advantages of comparing NMR in screening assays to that of other spectra, which is the limitation lacking in Yabuki et al, and

would therefore suggest to those of ordinary skill in the art that the Yabuki et al in view of the WO 97/18471 can be combine to teach the instant invention.

Yabuki describes using a dual amino acid-selective labeling method for investigating structures of proteins and protein complexes. Nothing in Yabuki suggests generating the two NMR spectra recited in the claims and subsequently comparing the two spectra to identify an interaction between a potential binder molecule having a molecular mass of from 50 to 1000 Da and a labeled polypeptide. As detailed above, Moore provides no suggestion or motivation to modify the technique of Yabuki to convert the method described therein into an assay to screen for interactions between a labeled polypeptide and a potential binder molecule having a molecular mass of from 50 to 1000 Da. Accordingly, Yabuki and Moore do not render obvious claim 1 or the claims that depend therefrom.

WO 97/18471 does not add what is lacking in Yabuki and Moore. WO 97/18471's disclosure of processes for identifying compounds would not have provided the requisite suggestion or motivation to cause the skilled artisan to so thoroughly alter the methods described by Yabuki so as to, instead of characterizing protein structures as is taught in detail in Yabuki, modify the labeling techniques described therein to be used for the altogether different purpose of carrying out a screening assay to identify potential binder molecules. Yabuki is not directed to screening assays and nothing in Moore or WO 97/18471, considered either alone or in combination, would have led the skilled artisan to (a) carry out the methods of Yabuki with a molecule having a molecular mass of from 50 to 1000 Da, and/or (b) fundamentally modify the techniques of Yabuki so as to screen to identify binder molecules.

In light of these comments, applicants respectfully submit that the combination of Yabuki, Moore, and WO 97/18471 do not render the claimed invention obvious and therefore request that the Examiner withdraw the rejection.

CONCLUSIONS

Applicants submit that all grounds for rejection have been overcome, and that all claims are now in condition for allowance, which action is requested.

Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 13425-047001.

Respectfully submitted,

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Jack Brennan
Reg. No. 47,443

Fish & Richardson P.C.
45 Rockefeller Plaza, Suite 2800
New York, New York 10111
Telephone: (212) 765-5070
Facsimile: (212) 258-2291